Asthma Exacerbations in Type 2 Diabetics with Asthma on Glucagon-like Peptide-1 Receptor Agonists

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Abstract: Rationale: Glucagon-like peptide-1 receptor (GLP-1R) agonists are approved to treat type 2 diabetes mellitus and obesity. GLP-1R agonists reduce airway inflammation and hyperresponsiveness in preclinical models. Objectives: To compare rates of asthma exacerbations and symptoms between type 2 diabetic adults with asthma prescribed GLP-1R agonists and those prescribed sodium-glucose cotransporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas or basal insulin for diabetes treatment intensification. Methods: Electronic health records-based new-user, active comparator, retrospective cohort study of patients with type 2 diabetes and asthma newly prescribed GLP-1R agonists or comparator drugs, January 2000-March 2018. Primary outcome was asthma exacerbations; secondary outcome was encounters for asthma symptoms. Propensity scores were calculated for GLP-1R agonist and non-GLP-1R agonist use. Zero-inflated Poisson regression models included adjustment for multiple covariates. Measurements and Main Results: Patients initiating GLP-1R agonists (n=448), SGLT-2 inhibitors (n=112), DPP-4 inhibitors (n=435), sulfonylureas (n=2,253) or basal insulin (n=2,692), were identified. At six months, asthma exacerbation counts were lower in persons initiating GLP-1R agonists (reference) compared to SGLT-2 inhibitors (incidence rate ratio [IRR], 2.98 [95% CI, 1.30 to 6.80]), DPP-4 inhibitors (IRR, 2.45 [95% CI, 1.54 to 3.89]), sulfonylureas (IRR, 1.83 [95% CI, 1.20 to 2.77]) and basal insulin (IRR, 2.58 [95% CI, 1.72 to 3.88]). Encounters for asthma symptoms were also lower among GLP-1R agonist users. Conclusions: Adult asthmatics prescribed GLP-1R agonists for type 2 diabetes had lower counts of asthma exacerbations compared to other drugs initiated for treatment intensification. GLP-1R agonists may represent a novel treatment for asthma associated with metabolic dysfunction.

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Impact: In this study of patients with asthma and type 2 diabetes, use of GLP-1R agonists for diabetes therapy was associated with fewer asthma exacerbations. These clinical, observational data build on preclinical data supporting a role for the GLP-1 metabolic pathway in asthma.

This article has an online data supplement, which is accessible from this issue's table of content online at **www.atsjournals.org**.

At a Glance

What is the current scientific knowledge on this subject?

Glucagon-like peptide-1 receptor (GLP-1R) agonists are approved to treat type 2 diabetes mellitus and obesity. GLP-1R agonists reduce airway inflammation and hyperresponsiveness in preclinical models.

What does this study add to the field?

In this study of patients with asthma and type 2 diabetes, use of GLP-1R agonists for diabetes therapy was associated with fewer asthma exacerbations. These clinical, observational data build on preclinical data supporting a role for the GLP-1 metabolic pathway in asthma.

AJRCCM Articles in Press. Published October 14, 2020 as 10.1164/rccm.202004-0993OC

Abstract

Rationale: Glucagon-like peptide-1 receptor (GLP-1R) agonists are approved to treat type 2 diabetes mellitus and obesity. GLP-1R agonists reduce airway inflammation and hyperresponsiveness in preclinical models.

Objectives: To compare rates of asthma exacerbations and symptoms between type 2 diabetic adults with asthma prescribed GLP-1R agonists and those prescribed sodium-glucose cotransporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas or basal insulin for diabetes treatment intensification.

Methods: Electronic health records-based new-user, active comparator, retrospective cohort study of patients with type 2 diabetes and asthma newly prescribed GLP-1R agonists or comparator drugs at an academic healthcare system, January 2000-March 2018. Primary outcome was asthma exacerbations; the secondary outcome was encounters for asthma symptoms. Propensity scores were calculated for GLP-1R agonist and non-GLP-1R agonist use. Zero-inflated Poisson regression models included adjustment for multiple covariates.

Measurements and Main Results: Patients initiating GLP-1R agonists (n=448), SGLT-2 inhibitors (n=112), DPP-4 inhibitors (n=435), sulfonylureas (n=2,253) or basal insulin (n=2,692), were identified. At six months, asthma exacerbation counts were lower in persons initiating GLP-1R agonists (reference) compared to SGLT-2 inhibitors (incidence rate ratio [IRR], 2.98 [95% CI, 1.30 to 6.80]), DPP-4 inhibitors (IRR, 2.45 [95% CI, 1.54 to 3.89]), sulfonylureas (IRR, 1.83 [95%

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CI, 1.20 to 2.77]) and basal insulin (IRR, 2.58 [95% CI, 1.72 to 3.88]). Healthcare encounters for asthma symptoms were also lower among GLP-1R agonist users.

Conclusions: Adult asthmatics prescribed GLP-1R agonists for type 2 diabetes had lower counts of asthma exacerbations compared to other drugs initiated for treatment intensification. GLP-1R agonists may represent a novel treatment for asthma associated with metabolic dysfunction.

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Introduction

Metabolic dysfunction represents a common and challenging comorbid asthma condition(1). Insulin resistance and metabolic syndrome are associated with asthma development(2, 3) and exacerbation risk(4). Among patients with asthma, those with higher BMI(5) or obesity(6) have higher medication and healthcare utilization and poor symptom control(7) suggesting that metabolic dysfunction contributes to asthma severity(8). Prior studies have shown that some medical therapies which improve insulin resistance (metformin, sulfonylureas) improve asthma control(9, 10). Limited observational data from patients with type 2 diabetes mellitus (type 2 DM) without respiratory disease, suggest that glucagon-like peptide-1 receptor (GLP-1R) agonists in combination with metformin may improve baseline pulmonary function(11). However, use of other diabetes therapies such as insulin and DPP-4 inhibitors do not impact incident asthma risk(12, 13). Therefore, therapies targeting metabolic pathways may be key to achieving asthma control for a significant proportion of individuals with asthma(14).

Glucagon-like peptide-1 (GLP-1) is a hormone stimulated by the ingestion of carbohydrates, fats, and proteins and secreted by the intestine and the central nervous system, thereby regulating metabolic, cardiovascular and neuroprotective activities(15, 16). GLP-1R agonists are FDA approved as part of a stepwise approach to treatment intensification beyond metformin for type 2 DM(17). As a class, the GLP-1R agonists potentiate insulin and suppress glucagon secretion in type 2 diabetics with low risk of hypoglycemia(18), decreased cardiovascular and renal risk(19) and lower all-cause mortality(20). GLP-1R signaling also

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promotes weight loss through delayed gastric emptying and increased satiety(18) leading to FDA approval for weight management in euglycemic patients (17).

The GLP-1R is found in lung epithelial and endothelial cells(11) underscoring a possible role for GLP-1 signaling in pulmonary disease(21). Administration of GLP-1R agonists in preclinical murine(22) and ex vivo models(11) significantly inhibits allergic and viral airway inflammation, decreasing airway eosinophilia, mucus production, and hyperresponsiveness(23, 24). However, the impact of GLP-1R agonist use on asthma exacerbations and asthma control (symptoms) in humans has not been assessed.

We analyzed real-world data from the electronic health records (EHR) of a large academic US health system to determine whether initiation of GLP-1R agonist therapy was associated with decreased asthma exacerbations and asthma symptoms compared with initiation of other therapeutics used for treatment intensification of type 2 DM among patients with asthma. Some of the results of these studies have been previously reported in the form of an abstract(25).

Methods

Patients, Settings and Data Source

The study used patient data between January 1, 2000 to March 1, 2018 from the Partners' Healthcare Research and Patient Data Repository (RPDR) that includes academic and community hospitals in the greater Boston, Massachusetts area. RPDR is a central data warehouse that stores clinical data across Partners Healthcare(26). Detailed medical record

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data elements extracted in this study included: demographics, diagnoses, laboratory tests, health maintenance, medications, problem lists, weight, height and body mass index (BMI).

Adult patients (≥18 years) meeting both asthma and type 2 DM definitions were included in the study (Figure 1). Asthma was defined as at least two separate encounters with a qualifying *International Classification of Diseases* (ICD) code or one asthma encounter with both a diagnosis code and an asthma medication prescription. Type 2 DM was defined as at least one encounter for type 2 DM or a hemoglobin A1c (HbA_{1c}) value ≥6.5, and a type 2 DM medication prescription. From this cohort we excluded patients with ICD diagnosis codes for diseases commonly treated with systemic steroids, chronic congestive heart failure, vocal cord dysfunction, and other respiratory diseases except chronic obstructive pulmonary disease (COPD), which we examined in our analysis. We also excluded patients with > two distinct encounters with type 1 DM codes. Inclusion and exclusion ICD codes criteria can be found in Table E1 in the online data supplement. Similar algorithms for inclusion and exclusion criteria have been previously validated at multiple institutions(27-30). Patients with a medication prescription and an ICD coded encounter diagnosis have a high rate of EHR data "completeness" in this dataset(31).

Study Design

We conducted a retrospective cohort study of routinely collected clinical data using a new user, active comparator design(32) to determine the association between GLP-1R agonist initiation and asthma outcomes. Active comparators included SGLT-2 and DPP-4 inhibitors, sulfonylureas and basal insulin (see Supplementary Table E2 for a complete listing of drug

AJRCCM Articles in Press. Published October 14, 2020 as 10.1164/rccm.202004-0993OC

names). Comparator drug classes were selected based on the American Diabetes Associations' (ADA) guidelines for treatment intensification of type 2 DM beyond first line therapy with metformin, diet and exercise (17). This stepwise approach is tailored to achieve glycemic targets and prevent diabetes complications.

Diabetics achieving glycemic control on first-line metformin monotherapy are clinically distinct from those requiring second-line or combination therapy by ADA guidelines; therefore, metformin monotherapy was not included as an active comparator. Concurrent diabetes medications including metformin were allowed. Given the potential effects of metformin on asthma control(10), metformin was included as a covariate in the analysis.

Exposure to any active comparator was defined as one prescription for the medication. Individuals were followed for six months from date of drug initiation as depicted in Figure E1 in the online data supplement. Duration of follow up was informed by medication adherence patterns in real-world clinical practice(33-35). We required all patients to have met both asthma criteria and type 2 DM criteria before drug initiation and to be alive at end of follow-up.

The primary outcome was a count of asthma exacerbations defined as a systemic (oral or intravenous) corticosteroid prescription(36). Further prescriptions within 7 days of the initial prescription were considered a single exacerbation event(37). The secondary outcome was a count of ICD coded emergency department (ED), inpatient and outpatient encounters for cardinal asthma symptoms: dyspnea, shortness of breath, wheeze, or cough (see Supplementary Table E3)(36, 38). Exploratory outcomes included counts of prescriptions for

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short-acting beta-agonists (SABA) in the same period and counts of routine encounters for asthma.

We calculated a propensity score representing the estimated probability of initiating a GLP-1R agonist versus an active comparator, for each participant(39). Baseline covariates included in the propensity score were: age, sex, race/ethnicity, year of drug initiation to account for drug availability, month of drug initiation categorized by regional seasons (December-February (Winter); March-May (Spring); June-August (Summer); September-November (Fall)) to account for seasonality of exacerbations and symptoms, insurance type, annual income (estimated from zip code), concurrent metformin use, Elixhauser chronic disease comorbidities (40), co-morbid COPD, and moderate or severe chronic kidney disease (CKD 3-5; defined as eGFR<60)(17). Post-baseline covariates (e.g. post-drug initiation BMI and HbA_{1c}) were not included(41). Propensity scores were then included as a covariate in zero inflated Poisson (ZIP) regression models. The relationships between covariates, exposure and outcome are modeled in a directed acyclic graph in the online supplement (Figure E2).

For each participant, the six months follow-up period began at new type 2 DM drug initiation. We expected a low event rate of asthma exacerbations based on Centers for Disease Control and Prevention data(42). ZIP models are selected when the occurrence of the outcome is rare employing a regression procedure specifically designed to account for positively skewed integer-valued distributions with a high incidence of zeros. The ZIP model first calculates a dichotomous outcome: the odds of a subject belonging to a class that always scores 0 vs. 1 on the outcome, e.g. any asthma exacerbation using logistic regression (“zero model”). The model

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then estimates the frequency of events (e.g. asthma exacerbation count) among subjects in the 1 class using a Poisson distribution, providing a count estimate from which a rate ratio can be calculated, and treatment conditions compared ("count model"). ZIP models were constructed with covariate adjustment for multiple confounders including season of drug initiation, baseline asthma severity in the 12 months prior to type 2 DM drug initiation categorized as mild (controlled without medications or with SABA or leukotriene receptor antagonist) versus moderate/severe (requiring inhaled corticosteroid alone or in combination with any other controller agent) based on prescription drug classes adapted from the 2018 Global Initiative for Asthma guidelines(43), smoking status, concurrent metformin prescription, and COPD, defined as ≥ 2 encounters at or within the 12 months prior to drug initiation. Examining the presence of co-morbid COPD coding within this asthma cohort reflects the recognition that in clinical practice patients with asthma may have features compatible with COPD, as in asthma-COPD overlap (ACO)(44) and accounts for co-coding in EHR data (45). COPD-only patients were excluded from this cohort by the asthma phenotype definition.

To test the robustness of the association between GLP-1R agonist use and asthma outcomes we added baseline BMI and HbA_{1c} in the propensity score. Change in BMI and change in HbA_{1c} over the follow-up period were included as covariates in the ZIP model as a sensitivity analysis.

In an additional sensitivity analysis, we examined those patients with more than one prescription for the initiated drug during the study period. We examined the effect of prescriptions for any DM drugs in the year preceding the 6-month study period as covariates to

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minimize confounding by longitudinal metabolic changes or order of treatment intensification. Patients with missing covariates were excluded from the sensitivity analyses. Each drug class has variable effect on weight and HbA_{1c}, both of which may be associated with asthma, and therefore imputed data was not used in any analysis.

In a pre-specified exploratory analysis, we examined prescriptions for SABAs and routine, non-exacerbation encounters for asthma in the follow-up period, applying the same model constraints and covariates. We additionally tested whether the findings in our primary analysis were robust for the moderate/severe asthma subgroup and never smokers.

Statistical significance was accepted at a two-sided *P*-value of ≤ .05. Statistical analyses were performed in SAS version 14.3 Cary, NC, USA. The study was approved by the Partners Institutional Review Board (protocol #2017P001730) prior to data collection.

Results

After inclusion and exclusion criteria were applied, our cohort included 448 new initiations of GLP-1R agonists, 112 of SGLT-2 inhibitors, 435 of DPP-4 inhibitors, 2,253 of sulfonylureas, and 2,692 of basal insulin for a total of 5,940 new initiations among 4,373 patients (Figure 1). Initiation did not differ by season across groups. Within the GLP-1R agonist class, liraglutide (53.1%) and exenatide (35.9%) were the most common drugs initiated. Table 1 shows the baseline characteristics of patients by drug initiation. New users of GLP-1R agonists were more likely to be younger and female. Baseline asthma severity was similar across the groups supporting there was therapeutic balance with regards to baseline asthma status prior

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to treatment intensification with GLP-1R agonists or comparators. 17% of asthma patients also had a prior encounter coded for COPD.

Analysis of Primary and Secondary Outcomes

For the primary outcome, asthma exacerbations within six months of drug initiation, GLP-1R agonist users had significantly fewer exacerbations compared to patients in all comparator groups in the multivariable count model (Table 2). As shown in Figure 2A, compared to GLP-1R agonist users, adjusted exacerbation rates were higher among SGLT-2 inhibitor, DPP-4 inhibitor, sulfonylurea and basal insulin. GLP-1R agonist users also had fewer encounters for asthma symptoms than DPP4-inhibitor, basal insulin and sulfonylurea groups (Table 2; Figure 2B). Unadjusted counts in each treatment group and unadjusted rates are presented in Supplementary Table E4. There were similarly higher symptom counts among 112 SGLT-2 inhibitor users that did not reach statistical significance. As metformin use was a predictor of fewer asthma exacerbations across groups, we included metformin as a covariate in the analysis; the effect of GLP-1R agonists on asthma exacerbations was independent of metformin. While GLP-1R agonist use was associated with decreased counts of exacerbations following initiation across all comparator groups, the odds of having zero exacerbations was increased by GLP-1R agonist use compared to DDP-4 inhibitor and insulin users, but not compared to sulfonylurea users or SGLT-2 inhibitor users (Supplementary Table E5). Odds of having zero encounters for asthma symptoms was not increased by GLP-1R agonist use across all groups.

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Sensitivity, Subgroup and Exploratory Analyses

In the propensity-score adjusted analysis inclusive of pre- and post-study period HbA_{1c} and BMI values, GLP-1R agonist users had statistically significant lower asthma exacerbation counts compared to all comparator groups (Table 3). The odds of having no exacerbation were not increased by GLP-1R agonist initiation compared to DPP-4 inhibitor, sulfonylurea and insulin users; SLGT-2 inhibitor users had increased odds of zero exacerbations (Supplementary Table E6). Missing covariate data was evenly distributed across the newer diabetes drug classes including GLP-1R agonist, SGLT-2 and DPP-4 inhibitors. Comparatively, basal insulin and sulfonylurea classes had more missing BMI and HbA_{1c} data. Patients missing any of these four values were excluded in this analysis.

Among users with ≥ 2 prescriptions for a given study drug during the six months study period (n=1,548), GLP-1R agonist users still had fewer asthma exacerbations compared to DPP-4 inhibitor (IRR, 2.31 [95% CI 1.08 to 4.91]; *P* = .03) and basal insulin (IRR, 2.88 [95% CI 1.63 to 20.85]; *P* = .002) groups with trends observed in sulfonylurea (IRR, 1.81 [95% CI 0.92 to 3.56]; *P* = .09) and SGLT-2 inhibitor (IRR, 1.75 [95% CI 0.25 to 12.23]; *P* = .57) groups (Supplementary Table E7).

The effect of GLP-1R agonists on asthma exacerbations was also independent of prior diabetes drug exposures across study groups. GLP-1R agonist users had fewer exacerbations compared to patients in all comparator groups in the count model including DPP-4 inhibitor (IRR, 2.51 [95% CI 1.58 to 3.98]; *P* = <.001), sulfonylurea (IRR, 1.84 [95% CI 1.21 to 2.78]; *P* =

AJRCCM Articles in Press. Published October 14, 2020 as 10.1164/rccm.202004-0993OC

.005), SGLT-2 inhibitor (IRR, 2.90 [95% CI 1.26 to 6.66]; *P* = .01), and basal insulin (IRR 2.64 [95% CI 1.76 to 3.98]; *P* = <.001) users.

The association between GLP-1R agonist use and decreased asthma exacerbations was robust in the moderate/severe asthma subgroup (Supplementary Table E8) despite a smaller sample size (n = 2,828). Among never smokers (n = 2,335) GLP-1R agonist users had fewer exacerbations compared to DPP-4 inhibitor, sulfonylurea, and basal insulin users but not SGLT-2 inhibitor users which was limited by small sample size (n = 69) (Supplementary Table E9).

We tested for the possibility of asthma medication non-compliance or degree of routine asthma healthcare utilization as drivers of asthma exacerbations. In exploratory analyses we found that there were no differences across groups compared to GLP-1R agonist users for routine asthma encounters or SABA prescriptions during the study period (Supplementary Table E10).

Discussion

In this EHR-based retrospective cohort study of asthmatic, type 2 diabetics requiring intensified type 2 DM therapy, those initiating GLP-1R agonists had fewer asthma exacerbations compared to those initiating alternate agents. There were no differences in baseline asthma severity across the groups and no difference in routine asthma care encounters during the study period. The propensity-score adjusted analysis accounted for important demographic confounders including sex, race/ethnicity as well as clinical confounders such as concurrent metformin use, seasonality, and smoking status. There were no differences in rate of drug

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initiation by individual month or by regional season. This was robust when also accounting for changes in HbA_{1c} and in BMI, suggesting that the observed association of GLP-1R agonists with decreased exacerbations is independent of improved glycemic control and weight loss.

Our secondary outcome analysis suggests that GLP-1RA initiators also have reduced asthma symptoms. We excluded diagnostic mimics of asthma, strengthening the specificity of these symptoms even in the context of the metabolic syndrome(46). Studies have shown that a history of asthma, as established in our study cohort, significantly increases the positive predictive value (PPV) of asthma symptoms as indicative of poor asthma control in EHR (47) even in the setting of obesity(48). Standardized patient-reported asthma control questionnaires such as the Asthma Control Test and Asthma Control Questionnaire use symptoms of "shortness of breath" and "wheeze" to measure symptom control(49, 50). Patients on GLP-1R agonists had fewer associated encounters coded with these symptoms compared to basal insulin and sulfonylurea users. This is distinct from routine encounters for asthma, which do not necessarily indicate any symptomatic state. No difference in symptom burden was seen compared to the SGLT-2 inhibitor group; however, these users had greater systemic steroid exposures due to asthma exacerbations during the same period which may have improved symptom control. While we excluded other respiratory diseases from our patient sample, we cannot exclude the possibility that these symptoms may be confounded by another disease process, such as atherosclerotic cardiovascular disease, also ameliorated by GLP-1R agonist use(19).

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Our data further suggest that GLP-1R agonists are associated with decreased exacerbation counts among patients with exacerbations, and particularly among the moderate/severe asthma subgroup, as GLP-1R agonist use was not consistently associated with increased odds of having zero exacerbations. This supports the observed clinical benefit of GLP-1RA among those with a more severe asthma phenotype. As our sample included patients with a range of asthma severity, we expected a high proportion of zero counts and low mean counts of exacerbations. This resulted in a modest absolute reduction in exacerbation rates which has implications for study design and sample size calculations for future prospective studies. Although a minority of asthma patients in the study were co-coded for COPD, they were predominantly classified as having moderate/severe asthma in line with prior estimates(44). The presence of COPD patients in the moderate/severe asthma group may reflect the clinical use of ICD codes to capture ACO which lacks specific diagnostic ICD codes. Clinical studies have traditionally excluded these patients(44) and future research is needed to ascertain phenotyping of these patients in the EHR in addition to the underlying pathobiology, to examine the potential role of metabolic pathways and therapeutic targets(14). Early research suggests that metformin, a first line diabetes therapy, may be beneficial for ACO highlighting the potential relevance of metabolic pathways in this group and warranting further investigation in this field(51). As this study's inclusion criteria only phenotyped asthma patients, excluding COPD-only patients, future research is needed to assess the impact GLP-1R agonist use on COPD-specific exposures and outcomes.

Strengths of this EHR analysis are the inclusion of BMI and HbA_{1c} data, clinically relevant covariates that may not be available in administrative datasets. The relationship of metabolic

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dysfunction and asthma represents an area of active investigation(8, 52). Other studies using administrative data have found that anti-diabetic therapies variably impact asthma in the setting of metabolic dysfunction; metformin attenuating asthma exacerbation risk(9, 10), consistent with our findings, and basal insulin associated with incident asthma(12). However, these studies were limited in their ability to address the impact of clinical covariates on their primary outcomes. These analyses point to a therapeutic association of GLP-1R agonists independent of metformin use, baseline and change in BMI, and glycemic control. Future areas of research include examining synergistic effects of anti-diabetes therapy, such as metformin and GLP-1R agonists, on pulmonary outcomes.

Limitations

This study relies on EHR data. EHR data are considered real-world data representing routine clinical care(39) that may be used to support supplementary indications for FDA-approved medications(53). However, there is considerable heterogeneity in approaches to disease phenotyping of EHR data(54-58) for asthma and DM, and we chose stringent phenotypes to address this limitation. There is potential for unmeasured confounding in this analysis. To minimize this, we additionally excluded patients who might routinely receive steroids and did not include prescriptions for inhaled corticosteroids in our outcome definition, consistent with core outcome measures for clinical asthma trials. Despite these steps, we could not exclude systemic steroids prescribed for an indication other than asthma exacerbation.

Similarly, data from the EHR reflects care sought by patients at sites within our health system. While our system is the largest in the region, and patients in this study met a high level

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of data completeness(31), it is not a closed system and there is no mechanism in place to flag outcomes that occur elsewhere but are missing in our EHR. Therefore, our outcome events may be underestimated across all drug exposures as patients may have sought care, particularly for acute episodes such as asthma exacerbations, at unaffiliated sites.

Finally, we took several steps to address confounders stemming from possible mechanistic links between metabolic and pulmonary dysfunction. We required a complete clinical data set for a sensitivity analysis that included baseline HbA_{1c}, baseline BMI and change in both parameters. The association for lower counts of asthma exacerbations among GLP-1R agonist users was robust across all the comparator groups, as previously discussed. Clinical data missingness was proportionally higher for basal insulin and sulfonylureas than the other three classes and we did not impute missing data. Missingness across years may be due to changes in EHR platforms or coding practice over time(39). Where weight and height were not both available at the same encounter, we carried forward height from prior visits to calculate BMI yet missing data for this important characteristic remains a weakness of this study. Insulin can be weight-promoting while GLP-1R agonists have a favorable weight loss profile. As obesity is associated with more poorly controlled asthma(6, 7) we cannot rule out residual confounding from weight in the basal insulin exposed population.

Conclusions

Among patients with asthma and type 2 diabetes requiring intensified type 2 DM therapy, those initiating GLP-1R agonists had lower counts of asthma exacerbations and asthma symptoms within six months of drug initiation compared to patients initiating other DM

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medications. Prospective human studies to validate these findings and to understand the mechanism(s) of the GLP-1R in the airway are needed to support the clinical selection of GLP-1R agonists for patients with asthma, with and without comorbid metabolic dysfunction.

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AJRCCM Articles in Press. Published October 14, 2020 as 10.1164/rccm.202004-0993OC

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Figure Legends

Figure 1. Selection of Patients from Electronic Health Records (EHR). Diagram depicts patient selection by EHR data as of March 2018. Some patients met more than one exclusion criteria. Final comparator groups included DPP-4 = dipeptidyl peptidase-4; GLP-1R = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2.

Figure 2. Incidence Rate Ratios and 95% CIs for Asthma Exacerbations and Asthma Symptom Encounters Among Patients with Type 2 Diabetes. Users of sodium–glucose cotransporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas and basal insulins were compared to glucagon-like peptide-1 receptor (GLP-1R) agonist users (reference group). **A**, GLP-1R agonist users have fewer asthma exacerbations compared to all comparator cohorts. Asthma exacerbations incidence rate ratios and 95% CIs are derived from zero inflated Poisson regression models. **B**, GLP-1R agonist users have fewer asthma symptoms compared to DPP-4 inhibitor, sulfonylurea and basal insulin groups. Asthma symptom encounter incidence rate ratios and 95% CIs are derived from zero inflated Poisson regression models.

AJRCCM Articles in Press. Published October 14, 2020 as 10.1164/rccm.202004-0993OC

Table 1. Baseline Characteristics of the Study Cohort

Patient baseline* characteristics	GLP-1R agonist users (n=448)	SGLT-2 inhibitor users (n=112)	DPP-4 inhibitor users (n=435)	Sulfonylurea users (n=2,253)	Insulin users (n=2,692)	*P*-value
Age, Mean (SD)	54(12.5)	60(11.4)	63.5(12.2)	59.5(14.1)	58.4(15)	<.001
Sex, No. (%)						<.001
F	323(72.1)	66(58.9)	286(65.7)	1387(61.6)	1,751(65)	
M	125(27.9)	46(41.1)	149(34.3)	866(38.4)	941(35)	
Race/ethnicity, No. (%)						<.001
White/Caucasian	298(66.5)	87(77.7)	300(69)	1,434(63.6)	1,714(63.7)	
Black/African Amer	58(12.9)	13(11.6)	47(10.8)	299(13.3)	382(14.2)	
Hispanic/Latino	46(10.3)	5(4.5)	43(9.9)	259(11.5)	332(12.3)	
Asian	3(0.7)	2(1.8)	14(3.2)	76(3.4)	36(1.3)	
Other/unknown	43(9.6)	5(4.5)	31(7.1)	185(8.2)	228(8.5)	
Insurance type, No. (%)						<.001
Medicaid	46(10.3)	7(6.3)	27(6.2)	204(9.1)	263(9.8)	
Medicare	172(38.4)	38(33.9)	196(45.1)	913(40.5)	1,000(37.1)	
Self	16(3.6)	4(3.6)	27(6.2)	308(13.7)	398(14.8)	
Commercial	210(46.9)	63(56.3)	178(40.9)	809(35.9)	1,011(37.6)	
Other	4(0.9)	0(0)	7(1.6)	19(0.8)	20(0.7)	
Annual income†, dollars						.01
<30,000	10 (2.3)	2 (1.8)	13(3.1)	88(4.0)	104(4.0)	
30,000-100,000	379(85.6)	92(82.1)	359(84.5)	1,939(87.1)	2,307(87.0)	
>100,000	54(12.2)	18(16.1)	53(12.5)	198(8.9)	240(9.1)	
Year of drug initiation, Average (SD) ‡	2 013.6(2.9)	2 015.7(1.2)	2 013.1(2.8)	2 010.3(4.4)	2 011(4.2)	<.001
Season§ of drug initiation, No. (%)						.21
Winter	95 (21.21)	16 (14.29)	107 (24.60)	517 (22.95)	658 (24.44)	
Spring	129 (28.79)	42 (37.50)	114 (26.21)	644 (28.58)	786 (29.20)	
Summer	109 (24.33)	32 (28.57)	110 (25.29)	529 (23.48)	621 (23.07)	
Fall	115 (25.67)	22 (19.64)	104 (23.91)	563 (24.99)	627 (23.29)	
Smoking status, No. (%)						<.001
Current	45(10)	9(8)	40(9.2)	353(15.7)	402(14.9)	
Never	208(46.4)	69(61.6)	205(47.1)	889(39.5)	964(35.8)	
Prior	168(37.5)	34(30.4)	148(34)	645(28.6)	791(29.4)	
Unknown	27(6)	0(0)	42(9.7)	366(16.2)	535(19.9)	
Chronic kidney disease (eGFR <60) ǁ, No. (%)						<.001
N	434(96.9)	109(97.3)	398(91.5)	2 163(96)	2,514(93.4)	

AJRCCM Articles in Press. Published October 14, 2020 as 10.1164/rccm.202004-0993OC

Y	14(3.1)	3(2.7)	37(8.5)	90(4)	178(6.6)	
COPD, No. (%)**						<.001
N	404(90.2)	107(95.5)	369(84.8)	1,907(84.6)	2,139(79.5)	
Y	44(9.8)	5(4.5)	66(15.2)	346(15.4)	553(20.5)	
Asthma severity††, No. (%)						.13
Mild (without recent medications)	160(35.7)	46(41.1)	153(35.2)	912(40.5)	1,040(38.6)	
Mild (with recent medications)	77(17.2)	18(16.1)	63(14.5)	289(12.8)	354(13.2)	
Moderate/Severe	211(47.1)	48(42.9)	219(50.3)	1,052(46.7)	1,298(48.2)	
Metformin use‡‡, No. (%)						<.001
N	202(45.1)	57(50.9)	185(42.5)	936(41.5)	1,504(55.9)	
Y	246(54.9)	55(49.1)	250(57.5)	1,317(58.5)	1,188(44.1)	
Elixhauser score, Mean (SD)	3.3(2.2)	3.1(2.4)	3(2.5)	2.9(2.2)	3.4(2.5)	<.001
BMI§§, Mean (SD)	39.5 (8.6)	34.7 (7.2)	34.4 (8.0)	35.4(8.5)	35.4 (10.5)	<.001
HbA_{1c} ll ll, Mean (SD)	8.4 (1.9)	8.2 (1.5)	8.1(1.6)	8.1 (1.8)	8.5 (2.2)	<.001
Change* in BMI, Mean (SD)**	-0.8 (2.7)	-1(2.3)	-0.2(8.7)	-0.2(3.0)	-0.5 (7.6)	.14
Change††† in HbA_{1c}, Mean (SD)	-0.7 (1.6)	-0.6 (1.1)	-0.6(1.4)	-0.8(1.8)	-1.0 (2.1)	.002

Light shading denotes included in propensity score. Dark shading denotes included in propensity score for the related sensitivity analysis only. For continuous variables the *P* value was calculated by one-way ANOVA; for categorial variables the *P* value was calculated by chi-square test.
*As of study drug initiation unless otherwise specified, for GLP-1R = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2; DPP-4 = dipeptidyl peptidase-4. Drugs in each class detailed in the online data supplement Table E2.
†Based on 5-digit zip code.
‡ Initial FDA approval for the newer diabetes classes include the following: GLP-1R agonists (2005), SGLT2-inhibitors (2013), DPP4-inhibitors (2006). Basal insulin and sulfonylurea classes were FDA approved before 2000.
§ December-February (Winter); March-May (Spring); June-August (Summer); September-November (Fall)
ll Defined as two or more *International Classification of Diseases* (ICD) codes for ESRD, chronic renal failure, or chronic kidney disease (CKD) stage 3-5 (eGFR <60) at or within 12 months before the initial prescription of study drugs.
** Defined as two or more encounters within 12 months prior to study drug initiation.
†† Defined by asthma medications prescribed within 12 months prior ("recent") to study drug initiation: mild-patient meets asthma definition but no asthma medication prescriptions in the 12 months prior to study drug initiation, or only short-acting beta agonists (SABA) or only leukotriene receptor antagonists (LTRA); moderate/severe- patients receiving an inhaled corticosteroid prescription alone or in combination with other controllers or biologics.
‡‡Defined as a prescription within 90 days prior to study drug initiation.
§§ Defined as a measurement closest to initial drug prescription, range included within 365 days of study drug initiation up until 14 days post-initiation.
ll ll Defined as a measurement closest to drug initiation, range included within 365 days of study drug initiation up until 14 days post-initiation.
*** Defined as the difference between baseline and end values. End BMI values included the measurement closest to the study end, range included 80 days from study drug initiation until 365 days post-study period end.
††† Defined as difference between baseline and end values. End HbA_{1c} values included the measurement closest to the study end, range included 80 days from study drug initiation until 365 days post-study period end.

AJRCCM Articles in Press. Published October 14, 2020 as 10.1164/rccm.202004-0993OC

Table 2. Primary and Secondary Asthma Outcomes*, by Type 2 Diabetes Treatment Groups

	Asthma exacerbations			Asthma symptoms		
Treatment groups†	**Incidence Rate Ratio**	**95% CI**	***P* value**	**Incidence Rate Ratio**	**95% CI**	***P* value**
GLP-1R (n=448)	*ref*			*ref*		
SGLT-2 inhibitor (n=112)	2.98	1.30 to 6.80	.01	1.44	0.72 to 2.88	.30
DPP-4 inhibitor (n=435)	2.45	1.54 to 3.89	<.001	1.71	1.14 to 2.57	.009
Sulfonylurea (n=2,253)	1.83	1.20 to 2.77	.005	1.73	1.21 to 2.47	.003
Basal insulin (n=2,692)	2.58	1.72 to 3.88	<.001	1.89	1.35 to 2.65	<.001

*Zero inflated Poisson regression model, count model (Poisson); both primary and secondary models reflect adjustment for significantly associated covariates including asthma severity, co-morbid chronic obstructive pulmonary disease, propensity score. The primary outcome model also reflects adjustment for metformin use which was negatively associated with exacerbations, but not symptoms.

† GLP-1R = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2, DPP-4 = dipeptidyl peptidase-4. Drugs in each class detailed in the online data supplement Table E2.

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Table 3. Sensitivity Analysis* for Asthma Exacerbations Outcome, Inclusive of Baseline and Change in Hemoglobin A1c (HbA_{1c}) and Body Mass Index (BMI)

	Asthma Exacerbations		
Treatment groups †	**Incidence Rate Ratio**	**95% CI**	***P* value**
GLP-1R (n= 271)	*ref*		
SGLT-2 inhibitor (n= 74)	2.95	1.19 to 7.31	.02
DPP-4 inhibitor (n= 224)	2.11	1.14 to 3.91	.02
Sulfonylurea (n= 1,007)	1.97	1.14 to 3.41	.02
Basal insulin (n= 1,015)	2.44	1.42 to 4.19	.001

*Zero inflated Poisson regression model, count model (Poisson); reflects adjustment for significantly associated covariates including co-morbid chronic obstructive pulmonary disease, metformin use, baseline HbA1c, change in BMI, propensity score.

†GLP-1R = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2, DPP-4 = dipeptidyl peptidase-4. Drugs in each class detailed in the online data supplement Table E2.

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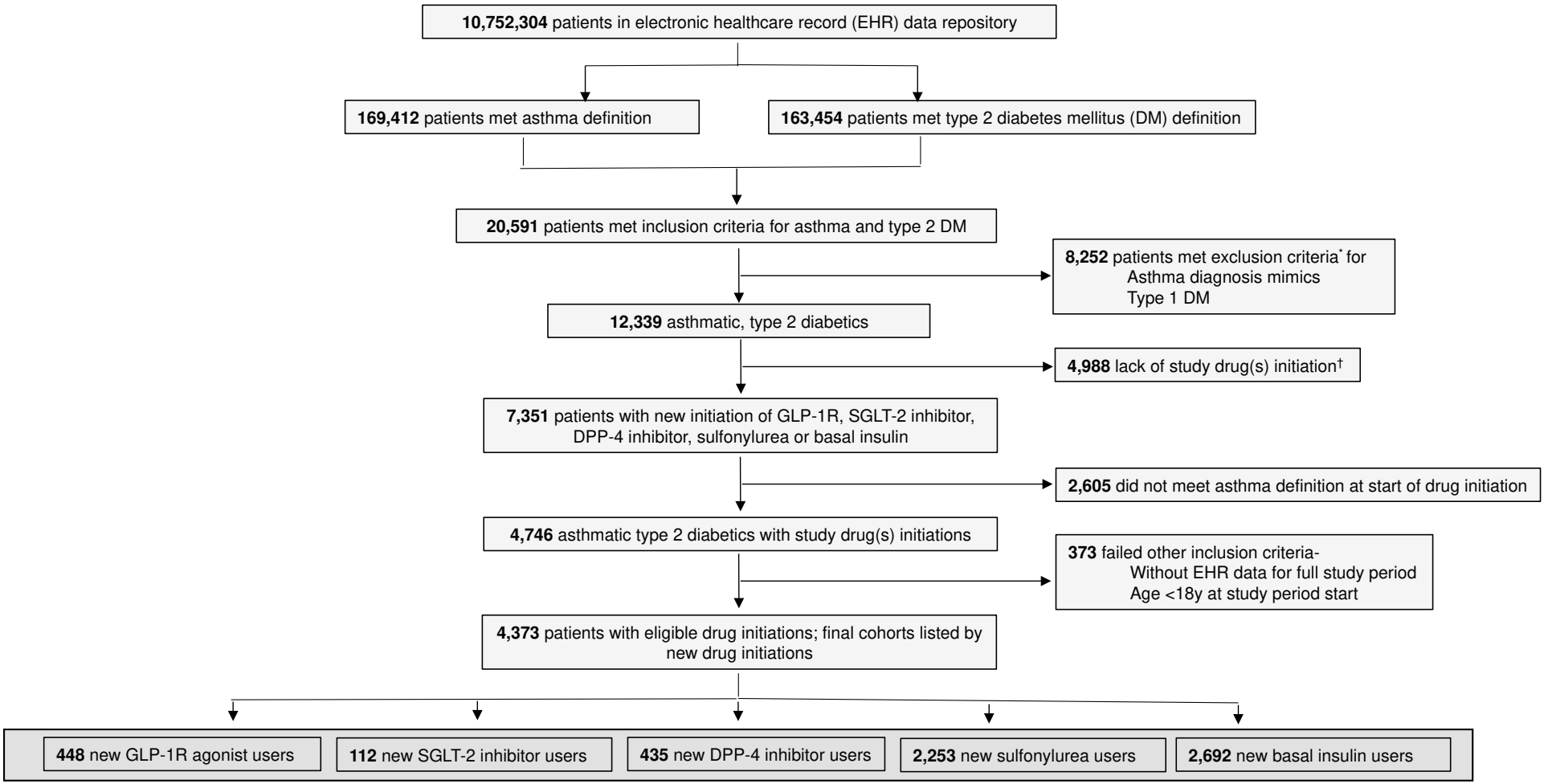
Figure 1



*Some patients met more than one exclusion criteria, as detailed in the online data supplement Table E1
†List of study drugs detailed in the online data supplement Table E2

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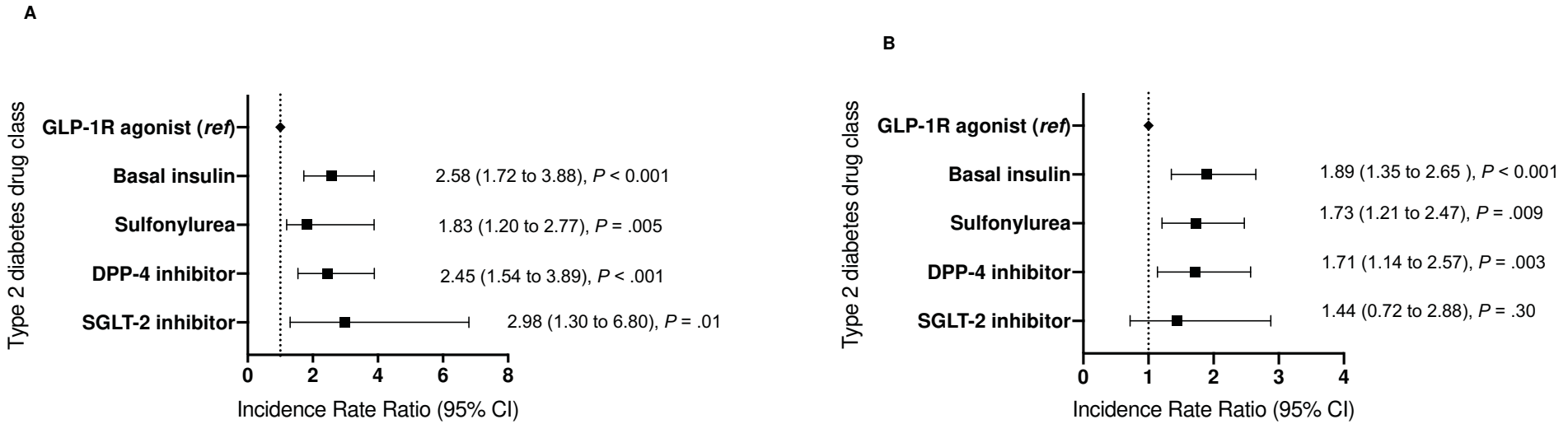
Figure 2



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Online Data Supplement

Asthma Exacerbations in Type 2 Diabetics with Asthma on Glucagon-like Peptide-1 Receptor Agonists

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Contents:

AJRCCM Articles in Press. Published October 14, 2020 as 10.1164/rccm.202004-0993OC

AJRCCM Articles in Press. Published October 14, 2020 as 10.1164/rccm.202004-0993OC

Table E1. Inclusion and Exclusion Definitions for Asthma and Type 2 Diabetes Mellitus

Inclusion Criteria	
Inclusion Diagnosis	**International Classification of Diseases (ICD)-9 and ICD-10 codes**
Asthma	493.x, J45.x
Type 2 diabetes mellitus (DM)	250.x0,250.x2. 249.xx, E08.xx, E09.xx, E11.xx, O24.1x
Asthma drug classes	**Asthma drug names***
Anticholinergics alone	Ipratropium bromide, tiotropium
Biologics	Omalizumab
Inhaled corticosteroid	Beclomethasone, trimacinolone, fluticasone, budesonide, mometasone, cliclesonide, flunisolide,
Inhaled corticosteroid combinations	Fluticasone-salmeterol, budesonide-formoterol, mometasone-formoterol, fluticasone-vilanterol
Leukotriene modifiers	Montelukast, zafirlukast, zileuton
Short acting beta agonists	Albuterol, levalbuterol, albuterol-ipratropium bromide
Type 2 DM drug classes	**Type 2 DM drug names***
Alpha glucosidase inhibitors	Acarbose, miglitol
Amylin mimetic	Pramlintide
Biguanides	Metformin
Basal insulin	Glargine, detemir, ultralente, degludec, lente, NPH
DPP-4 inhibitor†, ‡, §	Alogliptin, linagliptin, saxagliptin, sitagliptin,
GLP-1R agonist ll	Albiglutide, dulaglutide, exenatide, liraglutide
Meglitinides	Nateglinide, repaglinide
SGLT-2 inhibitor ‡.**	Canagliflozin, dapagliflozin, empagliflozin
Sulfonylurea‡	Glimepiride, chlorpropamide, acetohexamide, tolbutamide, glipizide, glyburide, tolazamide, glyburide, glipizide
Thiazolidinediones‡	Pioglitazone, rosiglitazone
Exclusion Criteria	
Exclusion Diagnosis	**ICD-9 and ICD-10 codes**
Type 1 diabetes	250.x1, 250.x3, E10.xx, O24.0x
Diseases impacting the respiratory system	
Allergic bronchopulmonary aspergillosis	518.6
Alpha 1-antitrypsin deficiency	273.4, E88.01
Aspiration syndromes	934.8, T17.8x
Benign neoplasms of bronchus or lung	212.3, D14.3x
Bronchiectasis	494.xx, J47
Bronchopulmonary dysplasia	770.7, P22.0, P27
Cancers of lymphatic and hematopoietic systems	200.xx-208.xx, C81-C96, D45, E85
Cerebral palsy	343.x, G80.x

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Table E1, continued.

Congenital airway and lung abnormalities	748.2-748.9, Q31-Q34
Chronic pulmonary heart diseases	416.x, I27.x
Cystic fibrosis and metabolic disorders	277.xx, V77.6, V83.81, E84.x, E88.3,
Disorders of diaphragm	519.4, J98.6
Extrinsic allergic alveolitis	495.x, J67
Lung involvement in other diseases classified elsewhere	517.x, D57.01, D57.01, D57.211, D57.411, D57.811, J17, J99
Motor neuron diseases	335.x, G12.x
Myopathies	359.x, G71.x, G72.x, G73.7
Pneumoconioses	500.x-508.x
Primary and secondary malignant neoplasm of airway, bronchus, lung or respiratory organs	160.xx to 165.xx, 197.0-197.3, C30-C34, C37- C39, C45, C78, J91.0
Pulmonary alveolar and parietoalveolar pneumonopathies	516.x, J84.x
Pulmonary fibrosis	515
Vocal cord and laryngeal disease	478.3x, 478.5, J38.0x, J38.2, J38.3
Disease often treated with systemic steroids	
Inflammatory arthropathies	714.x, M05.XX, M06.xx, M08.xx, M12.xxx
Organ or tissue transplant	V42.x, V49.83, V58.44, E878.0, 996.8x, T86.x, Y83.0, Z48.2xx, Z76.82, Z94.x, Z95.3, Z95.4
Post-transplant lymphoproliferative disorder	238.77, D47.Z1
Systemic lupus erythematosus, scleroderma, systemic sclerosis, dermatomyositis	710.x, M32-M36
Other asthma mimics	
Chronic congestive heart failure	428.XX, I50.22-23, I50.32-33, I50.42-43, I50.813, I50.84

*Agents available in the data set as of March 2018.

† Dipeptidyl peptidase-4.

‡ Includes formulations in combination with metformin.

§ Includes alogliptin formulation in combination with thiazolidinediones.

ǁ Glucagon-like peptide-1 receptor.

**Sodium-glucose costransporter-2.

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Table E2. Comparator Drugs Included in Study Design*

Drug class	Drug names
Basal insulin	Glargine, detemir, ultralente, degludec, lente, NPH
DPP-4 inhibitor†	Alogliptin, alogliptin–metformin, linagliptin, linagliptin–metformin, saxagliptin, saxagliptin–metformin, sitagliptin, sitagliptin–metformin
GLP-1R agonist‡	Albiglutide, dulaglutide, exenatide, liraglutide
SGLT-2 inhibitor§	Canagliflozin, canagliflozin–metformin, dapagliflozin, dapagliflozin–metformin, empagliflozin, empagliflozin–metformin,
Sulfonylurea	Glimepiride, chlorpropamide, acetohexamide, tolbutamide, glipizide, glyburide, tolazamide, glyburide-metformin, glipizide-metformin

*Among drugs available in the data set as of March 2018. Use of combined SGLT-2 inhibitor–DPP-4 inhibitor product was excluded (1 patient).

†Dipeptidyl peptidase-4.

‡Glucagon-like peptide-1 receptor.

§Sodium-glucose cotransporter-2.

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Table E3. Asthma Diagnoses and Medications Used for Outcome Definitions

Drug class	**Drug names***
Systemic (Oral and Intravenous) Steroids	Prednisone, methylprednisolone, dexamethasone
Asthma symptom	**International Classification of Diseases (ICD)-9 and -10 codes**
Cough	786.2, R05
Dyspnea	R06.00, R06.09
Shortness of breath	786.05, R06.02
Wheezing	786.07, R06.2

*Drugs available in the data set as of March 2018.

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Table E4. Unadjusted Counts and Rates of Asthma Exacerbations, by Treatment Group

Treatment group*	Count mean, (SD)	Unadjusted incident rate ratio	Adjusted† incident rate ratio
GLP-1R agonist (n=448)	0.17 (.58)	*ref*	*ref*
SGLT-2 inhibitor (n=112)	0.09 (.61)	0.53	2.98
DPP-4 inhibitor (n=435)	0.24 (.83)	1.42	2.45
Sulfonylurea (n=2,253)	0.22 (0.74)	1.27	1.83
Basal insulin (n=2,692)	0.33 (1.08)	1.93	2.58

*GLP-1R = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2, DPP-4 = dipeptidyl peptidase-4. Drugs in each class detailed in Table E2.

† For covariates in propensity score and zero-inflated Poisson model

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Table E5. Odds of No Asthma Exacerbation or No Asthma Symptom Encounter, by Treatment Group*

	Asthma exacerbations				Asthma symptoms			
Treatment group†	**Estimate**	**Odds Ratio**	**95% CI**	***P* value**	**Estimate**	**Odds Ratio**	**95% CI**	***P* value**
GLP-1R agonist (n=448)	*ref*				*ref*			
SGLT-2 inhibitor (n=112)	1.91	6.77	2.21 to 23.74	.001	0.46	1.58	0.63 to 3.98	.33
DPP-4 inhibitor (n=435)	0.77	2.14	1.15 to 4.00	.02	0.43	1.54	0.84 to 2.81	.12
Sulfonylurea (n=2,253)	0.45	1.57	0.91 to 2.71	.11	0.46	1.58	0.93 to 2.68	.09
Basal insulin (n=2,692)	0.54	1.71	0.99 to 2.93	.05	0.20	1.22	0.73 to 2.02	.45

* Zero inflated Poisson (ZIP), zero model (logistic).

†GLP-1R = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2, DPP-4 = dipeptidyl peptidase-4. Drugs in each class detailed in Table E2.

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Table E6. Odds of No Asthma Exacerbation by Treatment Group, Inclusive of Baseline and Change in Hemoglobin A_{1c} and Body Mass Index*

	Asthma exacerbations			
Treatment group †	**Estimate**	**Odds Ratio**	**95% CI**	***P* value**
GLP-1R agonist (n= 271)	*ref*			
SGLT-2 inhibitor (n= 74)	1.73	5.64	1.5 to 21.21	.01
DPP-4 inhibitor (n= 224)	0.67	1.95	0.80 to 4.73	.14
Sulfonylurea (n= 1,007)	0.37	1.44	0.67 to 3.13	.35
Basal insulin (n= 1,015)	0.23	1.25	0.58-2.70	.56

*Zero inflated Poisson (ZIP), zero model (logistic). Baseline and change over follow up period as defined in Table 1.

†GLP-1R = glucagon-like peptide-1 receptor; DPP-4 = dipeptidyl peptidase-4. Drugs in each class detailed in Table E2.

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Table E7. Asthma Exacerbations Among Initiators with More than One Prescription in Each Group During the Study Period, by Treatment Group*

	Asthma Exacerbations					
	Poisson model			*Logistic model*		
Treatment group†	**Incidence Rate Ratio**	**95% CI**	***P* value**	**Odds Ratio**	**95% CI**	***P* value**
GLP-1R agonist (n=133)	*ref*			*ref*		
SGLT-2 inhibitor (n=24)	1.75	0.25 to 12.23	.57	6.93	0.59 to 81.45	.12
DPP-4 inhibitor (n=112)	2.31	1.08 to 4.91	.03	1.88	0.65 to 5.46	.25
Sulfonylurea (n=603)	1.81	0.92 to 3.56	.09	1.23	0.49 to 3.10	.67
Basal insulin (n=676)	2.88	1.48 to 5.60	.002	1.39	0.56 to 3.46	.48

*Zero inflated Poisson (ZIP), count (Poisson) and zero (logistic) models; reflects adjustment for significantly associated covariates of comorbid COPD and asthma severity.

† GLP-1R = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2, DPP-4 = dipeptidyl peptidase-4. Drugs in each class detailed in Table E2.

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Table E8. Exploratory Analysis* for Asthma Exacerbations for Moderate/Severe Asthma Subgroup, by Treatment Group

	Asthma Exacerbations					
	Poisson model			*Logistic model*		
Treatment group†	**Incidence Rate Ratio**	**95% CI**	***P* value**	**Odds Ratio**	**95% CI**	***P* value**
GLP-1R agonist (n= 211)	*ref*			*ref*		
SGLT-2 inhibitor (n= 48)	3.94	1.65 to 9.42	.002	6.66	1.67 to 26.5	.007
DPP-4 inhibitor (n= 219)	2.54	1.44 to 4.46	.001	2.24	0.99 to 5.02	.05
Sulfonylurea (n= 1,052)	2.21	1.34 to 3.67	.002	1.58	0.77 to 3.24	.21
Basal insulin (n= 1,298)	3.05	1.85 to 5.01	<.001	1.63	0.80 to 3.33	.18

*Zero inflated Poisson (ZIP), count (Poisson) and zero (logistic) models; reflects adjustment for significantly associated covariates of comorbid COPD.

†GLP-1R = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2, DPP-4 = dipeptidyl peptidase-4. Drugs in each class detailed in Table E2.

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Table E9. Exploratory Analysis for Asthma Exacerbations in a Never Smoker Subgroup, by Treatment Group

	Asthma Exacerbations					
	Poisson model			*Logistic model**		
Treatment group†	**Incidence Rate Ratio**	**95% CI**	***P* value**	**Odds Ratio**	**95% CI**	***P* value**
GLP-1R agonist (n=208)	*ref*			*ref*		
SGLT-2 inhibitor (n=69)	0.36	0.003-48.30	.68	-	-	-
DPP-4 inhibitor (n=205)	3.97	1.0-14.22	.05	5.46	0.29-102.82	.26
Sulfonylurea (n=889)	4.17	1.18-14.78	.03	4.60	0.21-99.9	.33
Basal insulin (n=964)	4.94	1.32-18.44	.02	4.56	0.21-101.43	.34

*Zero inflated Poisson (ZIP) count model. SGLT-2 inhibitor sample size was too small to calculate event odds in the logistic model.

†GLP-1R = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2, DPP-4 = dipeptidyl peptidase-4. Drugs in each class detailed in Table E2.

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Table E10. Exploratory Analysis* for Asthma Encounters and Short-acting Beta Agonist Prescriptions, by Treatment Group

	Asthma Encounters			*Short-acting Beta Agonists*		
Treatment group†	**Incidence Rate Ratio**	**95% CI**	***P* value**	**Incidence Rate Ratio**	**95% CI**	***P* value**
GLP-1R agonist (n=448)	*ref*			*ref*		
SGLT-2 inhibitor (n=112)	1.01	0.64 to 1.58	.98	.70	0.47 to 1.04	.08
DPP-4 inhibitor (n=435)	0.77	0.56 to 1.04	.09	.88	0.73 to 1.08	.23
Sulfonylurea (n=2,253)	0.98	0.80 to 1.20	.85	.93	0.85 to 1.02	.13
Basal insulin (n=2,692)	1.13	0.93 to 1.37	.21	1.05	0.93 to 120	.40

*Zero inflated Poisson (ZIP), count (Poisson) model.

†GLP-1R = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2, DPP-4 = dipeptidyl peptidase-4. Drugs in each class detailed in Table E2.

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Figure E1. Study Design Data extracted from electronic health records generated between years January 2000-March 2018. Six-month study period begins at GLP-1R agonist or comparator drug new initiation. GLP-1R = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2; DPP-4 = dipeptidyl peptidase-4.

Figure E2. **Directed acyclic graph** summary for variables considered in Table 1. Box A includes baseline variables associated with the exposure. Box B includes baseline variables identified as potential confounders, associated with both exposure and outcome (asthma exacerbation). Box C includes variables associated with the outcome.

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Figure E1.

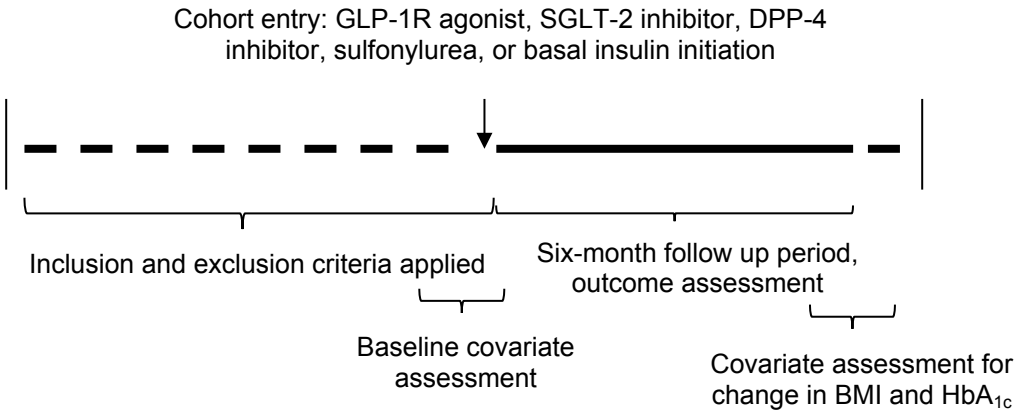

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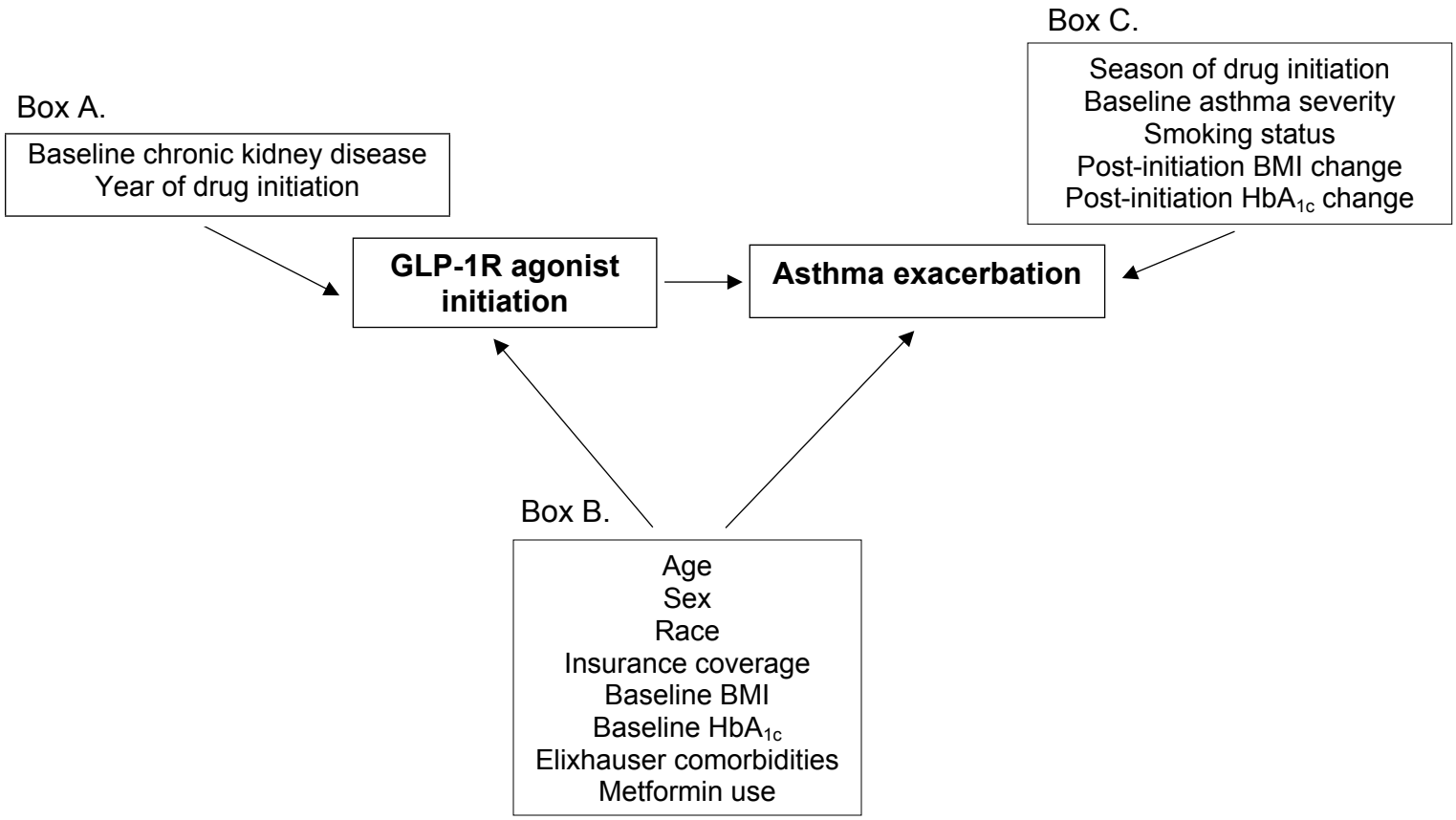
Figure E2.



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